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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT		ATTY. DOCKET NO.
08/886,044	06/30/97	BHATTACHARJEE	A	71007/137

EXAMINER	
LORING, S	
ART UNIT	PAPER NUMBER
1641	20

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DATE MAILED: 03/19/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 6/30/97 and 3/31/97

☐ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~or thirty days,~~ whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-3, 5-9, and 11-18 is/are pending in the application.
Of the above, claim(s) 11-14 and 18 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-3, 5-9, and 15-17 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

40517

1. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group 1640, Art Unit 1641. Additionally, the Examiner on this application has changed. Please address all future responses and correspondence to Examiner Susan A. Loring.

2. The instant application has been filed under 37 CFR 1.62 as a continuation of SN 08/230,402, filed April 20, 1994, now abandoned. Applicant is required to amend the continuity of the first paragraph of the specification to reflect the abandoned status of SN 08/230,402.

3. Claims 1-3, 5-9 and 11-18 are pending. Claims 4 and 10 have been canceled. Claims 11-14 and 18 are drawn to non-elected inventions and are withdrawn from consideration. Claims 1-3, 5-9 and 15-17 will be examined in this Office Action. Applicant has not submitted a Preliminary Amendment, but the claims previously filed on March 31, 1997 under 37 CFR 1.116, in the prior application, have been entered.

4. The Declarations submitted by Drs. Steven Opal and Alan Cross have been substantively addressed by the previous Examiner in the Advisory Action (paper 17) mailed 5/15/97. As the Declaration by Dr. Steven Opal is unsigned and a signed copy has not been received, this Declaration will not be further considered or commented on until a signed Declaration is received and made of record in this application.

5. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 has been improperly amended in paper 15 as applicant has included the limitation "(ii) a purified "detoxified" outer membrane protein (OMP) ". The limitation "detoxified" has been improperly inserted into the claim, as it has not been properly indicated to be amendatory material by underlining. The specification discloses "purified outer membrane protein derived from N. meningitidis" (page 3, lines 19-20 and 31-32; page 4, lines 1-2 and lines 29-30; Example 2, pages 8-10, for example), but does not disclose any teaching for producing a "detoxified" OMP. This limitation is considered unsupported and as such is new matter.

Claim 1 has been amended to include the recitation "wherein the antibody produced by said vaccine is not bacteriocidal". This negative limitation is considered new matter, as the specification, Example 9,

indicates that "the post-immune sera from the rabbits of Example 9, indicates that "the post-immune sera from the rabbits of Example 8 was bacteriocidal." As shown in Table 4, this vaccine elicited significant increases (4 to 32 fold) in bactericidal titer against both homologous and heterologous strains". Example 8 shows rabbits immunized with the J5 DLPS-NMGBOMP non-covalent complex vaccine. The amendment to include this limitation is considered new matter, as the specification clearly indicates that the complex induces bacteriocidal antibodies and no where in the instant specification can support be found where the antibodies are not considered bacteriocidal when using the complex.

Claim 1 has been amended to include the recitation "devoid of O-oligosaccharide side chains" derived from *E. coli* J5 strain, but has failed to point to specific support within the instant specification. The preparation of lipopolysaccharide from *E.coli* J5 was purchased from List Biological Laboratories. The specification further discloses that "this preparation contained less than 1% protein and less than 1% nucleic acid as determined by absorbances at 260/280 nm." The specification fails to contain any written description that this preparation is "devoid of O-oligosaccharide side chains" as now claimed. Applicant is encouraged to point to specific support within the instant specification for this amendment or remove this limitation from the claim.

6. Claims 1-3, 5, and 15-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 1 has been amended to recite "A vaccine, effective in actively or passively immunizing a subject against infection by heterologous Gram-negative bacteria or against lipopolysaccharide (LPS) endotoxin-mediated pathology by the production of an antibody, comprising a non-covalent complex between (I) purified, detoxified LPS endotoxin devoid of O-oligosaccharide side chains derived from *E. coli* J5 strain and (ii) a purified, detoxified outer membrane protein (OMP) derived from *N. meningitidis*, wherein the antibody produced by said vaccine is not bacteriocidal." Claims 2-3, 5 and 15-17 depend from claim 1. Claim 1 has been amended to add "or passively" but the specification fails to support this limitation in the manner in which this claim is drawn. The specification discloses "a subject can be actively immunized with a non-covalent vaccine comprising a complex between purified *E. coli* LPS and purified outer membrane protein derived from *N. meningitidis*. Serum or plasma from an actively immunized subject, or IgG isolated therefrom, can be administered to a second subject to confer on the latter a passive protection against Gram-negative bacterial infections and LPS-mediated pathology." The specification clearly does not intend, disclose, or misrepresent the use of a

vaccine comprising a complex between (I) and (ii) which is effective for passively immunizing a subject. The specification contemplates the serum obtained after vaccine immunization from a first subject to be administered to a second subject to potentially confer protection to a second subject. This is not the same as the intended meaning set forth in claim 1.

7. The rejection of claims 1-3, 5-9 and 15-17 under 35 USC 112, first paragraph, because the specification, while being enabling for a method of actively immunizing a rabbit or neutropenic rat against infection by heterologous Gram-negative bacteria and LPS endotoxin-induced pathology and a vaccine effective in the claimed method , does not reasonably provide enablement for a method of actively immunizing any subject (said subject to include humans) against infection by heterologous Gram-negative bacteria and LPS endotoxin-induced pathology and a vaccine effective in the claimed method, as set forth in the previous Office Action (paper 13) and the Advisory Action (paper 17), is maintained for reasons of record .

The specification discloses preparation methods for purified, detoxified *E. coli* J5 LPS (Example 1) and purified outer membrane protein derived from *N. meningitidis* group B (Example 2); preparation of a non-covalent complexes (Examples 3 and 4); pyrogenicity testing of the J5 DLPS-NMGBOMP complex (Example 5); immunogenicity testing of the complex vaccine in New Zealand white rabbits (Examples 7 and 8); bactericidal antibody response from post-immune sera from rabbits of Example 8 (Example 9); enhanced cross-reactive binding of IgG from post-immune (Example 8) sera of rabbit (Example 10); and finally protection of rats using the neutropenic rat model of sepsis. The specification fails to provide evidence correlating the data disclosed from the rabbit and rat models with the scope of the claimed invention, such that the evidence disclosed is predictive of reactivity in humans.

Applicants submitted a Declaration by Dr. Steven Opal to support the enablement of the claimed invention. The Declaration was addressed by the previous Examiner in paper 17. The Declaration by Dr. Opal cannot be further considered as a signed Declaration has not been made of record. The rejection as set forth above deals with the lack of evidence for the claimed method and vaccine to enable the scope of said vaccine and method. All of the examples disclosed in the instant specification fail to correlate active immunization of humans, as no convincing evidence has been provided indicating that the neutropenic rat or the rabbit animal model are predictive of successful treatment in humans against infection by heterologous Gram negative bacteria or against lipopolysaccharide endotoxin-mediated diseases. The immune system is a complex system that is not controlled or modulated by the manipulation or inhibition of one single factor.

Treatment of most immune complex diseases are not dependent on a single function for successful treatment. The Examples provided within the instant specification fail to provide convincing correlating evidence to enable the claimed method and vaccine for therapeutic treatment of the recited diseases. If applicant wishes to amend the claimed invention to a rabbit and/or neutropenic rat, than, in fact, the invention would be sufficiently enabled. In the absence of convincing evidence this rejection is maintained for reasons of record.

Undue experimentation would be required to practice the invention as claimed due to the quantity of experimentation necessary, the limited amount of guidance, the presence or absence of limited number of working examples in the specification, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. Ex parte Foreman, 230 USPQ 546, 547 (Bd. Pat. Appls. and Interf. 1986)

8. The rejection of claim 1 under 35 USC 102(b) as being anticipated by Zollinger et al (US PAT 4,707,543), as set forth in the previous Office Action (paper 13) on page 5 and the Advisory Action (paper 17) on page 5, is withdrawn in view of applicants amendments to the claim.

9. The rejection of claims 1-3, 5-9 and 15-17 under 35 USC 103 as being unpatentable over Zollinger et al (US PAT 4,707,543), is maintained for reasons of record.

Claim 1 is drawn to "A vaccine, effective in actively or passively immunizing a subject against infection by heterologous Gram-negative bacteria or against lipopolysaccharide (LPS) endotoxin-mediated pathology by the production of an antibody, comprising a non-covalent complex between (I) purified, detoxified LPS endotoxin devoid of O-oligosaccharide side chains derived from *E. coli* J5 strain and (ii) a purified, detoxified outer membrane protein (OMP) derived from *N. meningitidis*, wherein the antibody produced by said vaccine is not bacteriocidal." Claims 2-3 and 5 depend from claim 1 and claims 15-17 drawn to an immunogenic composition comprise the vaccine of claim 1. Claims 6-9 are drawn to a method of actively immunizing a subject using the vaccine of claim 1.

Applicants have provided a Declaration by Dr. Alan Cross arguing this rejection. The Declaration by Dr. Cross is summarized as follows: 1) the present invention is drawn to a vaccine which protects against heterologous infections and the Zollinger Patent is directed to vaccines against homologous infections; 2) the Zollinger Patent does not teach cross-protection, passive immunization, or heterologous protection; 3) the concepts of the protective antibodies and the types of antibodies of the Zollinger Patent are different from the instant invention; and 4)the Zollinger Patent fails to teach any of the animal models disclosed in the instant

invention. The Declaration by Dr. Cross is not deemed to be convincing for the following reasons. First, applicant is reminded that this rejection is made under 35 USC 103 (obviousness) not 35 USC 112, first paragraph (insufficient enablement for the scope of the claimed invention). Zollinger et al teach the production of purified outer membrane protein and purified detoxified LPS. The term polysaccharide includes lipopolysaccharide and capsular polysaccharide. The detoxified lipopolysaccharide outer membrane complexes could be either noncovalently or covalently bonded. (Col. 4, lines 15-22). Zollinger further teaches "(t)he detoxified polysaccharide-outer membrane protein complexes prepared according to applicants' novel process of this invention induces immune response to bacterial infections. More specifically, evidence indicates that these complexes have activity against bacterial infections caused by gram-negative bacteria including *Neisseria meningitidis* group B, *Haemophilus influenza* type b, *Neisseria gonorrhoeae*, *Escherichia coli*, and *Pseudomonas aeruginosa*." (Col 12, lines 17-25) In view of the teaching of Zollinger for producing each of the components of the vaccine and teaching induction of an immune response to heterologous bacterial infection, it would have been obvious to one of ordinary skill in the art at the time of applicants' invention to produce the instantly claimed vaccine and actively immunize a subject.

The invention has been shown to be clearly obvious over the prior art of record and applicant has provided no evidence within the instant specification to demonstrate that the claimed vaccine and method of actively immunizing differs in any unexpected or unobvious manner from that which one of ordinary skill in the art would have expected to obtain upon combining the teachings of the references. Thus, the claimed invention as a whole was prima facie obvious to one of ordinary skill in the art at the time it was made in the absence of sufficient evidence to the contrary.

10. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Susan A. Loring whose telephone number is (703)308-3998.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SUSAN A. LORING
PRIMARY EXAMINER
GROUP 1800

March 16, 1998